

**Opinion of the Scientific Panel on Food Additives,
Flavourings, Processing Aids and Materials in Contact with Food
on a request from the Commission related to**

Creatine monohydrate for use in foods for particular nutritional uses

Question number EFSA-Q-2003-125

adopted on 17 February 2004

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food has been asked to provide a scientific opinion, based on its consideration of the safety and bioavailability of the nutrient source, creatine monohydrate, when used in the manufacture of foods for particular nutritional uses.

Creatine occurs in the body, with higher concentrations in muscles. It can be obtained from the diet, predominantly meat and fish, and can be synthesized endogenously in the pancreas, kidneys and the liver from the amino acids glycine, arginine and methionine at the rate of 1-2 g/day.

A previous opinion from Scientific Committee on Food (SCF) expressed in 2000 considered the existing evidence as insufficient to provide reassurance about the safety of creatine supplementation involving high loading doses. It was indicated that little information exists on long-term safety of creatine, and that adequate quality control and adequate specifications for food grade materials should be developed.

A high purity (minimum 99.95%) source of creatine monohydrate is considered here. It is produced under conditions that prevent microbiological and heavy metals contamination, and acceptable limits for the impurities creatinine, dicyandiamide and dihydro-1,3,5-triazine are obtained.

The safety and bioavailability of the requested source of creatine, creatine monohydrate in foods for particular nutritional uses, is not a matter of concern provided that there is adequate control of the purity of this source of creatine with respect to dicyandiamide and dihydro-1,3,5-triazine derivatives. The Panel endorses the previous opinion of the SCF that high loading doses of creatine should be avoided. Provided high purity creatine monohydrate is used in foods for particular nutritional uses, the Panel considers that the consumption of doses of up to 3g/day of supplemental creatine, similar to the daily turnover rate of creatine, is unlikely to pose any risk.

KEY WORDS

Creatine monohydrate, Foods for particular nutritional uses (FPNU), CAS Registry Number 6020-87-7

BACKGROUND

Creatine (N-(aminoiminomethyl)-N-methyl glycine) is an endogenous substance, with the highest concentrations in the skeletal muscle (approximately 95% of the total creatine pool) and in the heart muscle. It occurs in foods such as meat, fish and other animal products. A typical diet supplies 1-2 grams of creatine daily. In the absence of dietary creatine it may also be formed endogenously by liver, kidney and pancreas from the amino acids glycine, arginine and methionine at the rate of 1-2 g/day (see references in SCF 2000a).

A report on "the composition and specification of food intended to meet the expenditure of intense muscular effort, especially for sportsmen" was adopted by the SCF in 2000 (SCF 2000b). It included creatine as a possible component of this particular food but the report addressed mainly efficacy and not safety issues.

Subsequently, an opinion of the SCF on safety aspects of creatine supplementation was expressed in 2000 (SCF 2000a). The SCF considered that supplementation with 2-3g/day, which are similar to the daily turnover rate of 2g/day, are unlikely to pose any risk.

The nutritional substances that may be added as sources of certain categories of nutrients are subject to Commission Directive 2001/15/EC on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (EC 2001) or directives on specific categories of foods for particular nutritional uses.

The SCF was asked in November 2001 to consider the safety of a number of substances as sources of nutrients for foods for particular nutritional uses (FPNUs). Due to deficiencies in the original dossiers submitted, the evaluations could not be completed under the SCF mandate and continuation of this work now falls to the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. Creatine monohydrate (CM) as a source of creatine was one of the substances.

Evaluation of CM as a nutrient source for creatine in practice includes evaluation of the purity of the source and the bioavailability of creatine from the source. Apart from the impurities the safety of CM is considered to be similar to that of creatine, the safety of which has been evaluated by the SCF before (SCF 2000a).

TERMS OF REFERENCE

The Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of the nutrient source, creatine monohydrate, when used in the manufacture of foods for particular nutritional uses.

ASSESSMENT

Composition, specifications and properties.

CM has CAS-number 6020-87-7; its formula is $C_4H_9N_3O_2 \cdot H_2O$ and it has a molecular weight of 149.1. CM solubility in water is 1.3g/100g at 20 °C. CM contains 12.1 % water of crystallization. According to the petitioner (IDACE 2003) it is of high purity (typically 99.99%, min. 99.95%). The product is said to comply with the following specifications: creatinine maximum 100 mg/kg, dicyandiamide maximum 50 mg/kg and dihydro-1,3,5-triazine not detectable (lower than the detection limit of 4.5 mg/kg). It is produced under conditions, which prevent microbiological and heavy metals (maximum 10 mg/kg) contamination (IDACE 2003). Maximum levels of each of Hg,

Cd, Pb or As are 1 mg/kg. The shelf life of CM is minimum 36 months from the date of manufacture, in an unopened container at room temperature.

Manufacturing process

The manufacturing process of this product (chemical synthesis from cyanamide and sarcosine) is described by the petitioner (US patent 5,719,319).

The petitioner indicates that the reaction conditions as well as the treatment of the crude CM are crucial for the quality of the product. Inferior starting materials or insufficient amount of water during "recrystallization" result in increased amounts of impurities, such as dicyandiamide, creatinine and dihydro-1,3,5-triazine derivatives.

Proposed use

The proposed use for CM as a source of creatine is in food for particular nutritional uses intended for all age groups. The petitioner provided no information on intended levels of use.

Exposure

The petitioner gives no information on exposure to CM. Typical doses of pure creatine monohydrate used in scientific studies range between 2-25 grams per person per day for an average adult and the dosing regimens suggested by the manufacturers of creatine are 20 g/day for 3 to 7 days and then 2-5 g/day as a maintenance dose (see SCF 2000a).

Existing authorizations

It is reported (IDACE, 2003) that CM has been used as a supplement, for example in Germany (10g/day) and the USA. In the USA CM is being used as a dietary supplement under the conditions of the Dietary Supplement Health and Evaluation Act (DSHEA) and it can be purchased over the counter in health food stores and pharmacies (IDACE 2003).

Biological and toxicological data

Bioavailability and interactions

According to the petitioner, ingestion of 5 g of CM in humans produces an increase in plasma creatine over 500 μ M (0.75 g/l) one hour after ingestion, which indicates that CM is bioavailable.

Toxicological information:

Only a limited summary of toxicological information was supplied by the petitioner reporting that the acute toxicity of CM is low (LD_{50} in the rat is higher than 2 g/kg), and that it is not mutagenic in the Ames test. CM has been tested in a 28-day rat study in which no treatment related adverse effects were reported after dose levels up to 2 g/kg bw/day.

A recent study (Kreider *et al.* 2003) examined the effects of long-term creatine supplementation on several serum, whole blood, and urinary markers of clinical health status in athletes (range 18-23 years), over a 21-month period. Subjects were given 15.75 g/day of CM for 5 days and an average of 5 g/day thereafter in 5-10 g/day doses. A comprehensive quantitative clinical chemistry set of parameters was determined on serum and whole blood samples (metabolic markers, muscle and liver enzymes, electrolytes, lipid profiles, haematological markers, and lymphocytes). In addition,

urine samples were used to assess clinical status and renal function. Baseline and the subjects' final blood and urine samples were analyzed. At the end of the study, subjects were categorized into groups that did not take creatine ($n = 44$) and subjects who took creatine for 0-6 months (mean 4.4 \pm 1.8 months, $n = 12$), 7-12 months (mean 9.3 \pm 2.0 months, $n = 25$), and 12-21 months (mean 19.3 \pm 2.4 months, $n = 17$). There were no significant differences among the groups in the 54-item panel of quantitative blood and urine markers assessed. The results indicate that creatine supplementation for up to 21 months does not appear to adversely affect markers of health status in athletes undergoing intense training in comparison to athletes who do not take creatine (Kreider *et al.* 2003).

A tolerable daily intake (TDI) of 1 mg/kg bw/day has been established for dicyandiamide used as a monomer for food packaging material (SCF 1995).

Discussion

No specific assessment of exposure of CM was considered necessary provided that the intake of creatine is within the amounts judged unlikely to pose any risk (2-3 g/day).

The bioavailability of CM is considered to be the same as that of creatine.

Daily intake of 3 g of CM containing the highest level of impurities specified would lead to an intake of less than 150 μ g of dicyandiamide/day. Considering a human body weight of 60 kg, such an intake would be less than 2.5 μ g/kg bw/day of dicyandiamide, i.e. 0.25% of the TDI of 1 mg/kg bw/day established for this substance for use as a monomer for food packaging material (SCF 1995). Dihydro-1,3,5-triazine derivatives were reported to be not detectable in the CM preparation under consideration (detection limit of 4.5 mg/kg).

The safety of CM is therefore considered to be similar to that of creatine, which has been considered earlier by the SCF (SCF 2000a) who concluded the following:

“Although many efficacy trials have studied the effects of creatine, large-scale, well-controlled studies are lacking. Available results observed in highly trained athletes cannot necessarily be extrapolated to the general public. Little information exists on the short-term or long-term safety of creatine and adequate quality control of the commercially marketed creatine is lacking. Adequate specifications for food grade materials should be developed.

Although no important adverse effects have been reported in the efficacy trials, such evidence is insufficient to provide reassurance about the safety of creatine supplementation involving high loading doses: there are doubts about safety in relation to kidney function; studies on tissues in which creatine is known to concentrate are lacking; effects on endogenous creatine synthesis upon cessation of supplementation are also not well studied. For these reasons the Committee considers that high loading doses should be avoided. Consumption of lower doses of around 3g/day are similar to the daily turnover rate of 1-2g/day and are unlikely to pose any risk.

Future studies should evaluate short- and long-term effects of oral creatine on renal and hepatic systems as well as those organs where creatine plays a metabolic role. Such studies should include people who are not highly trained.

CM has been tested in a 28-day rat study. No treatment related adverse effects were reported after dose levels up to 2 g/kg bw/day.

The results of a recent human study indicate that CM intake (\sim 5 g/day for up to 21 months) appears to be safe for athletes engaged in intense training and competition. However, this does not give reassurance about potential long-term effects of high doses of CM in people who are not highly trained or belong to other population subgroups.

CONCLUSION

The safety and bioavailability of the requested source of creatine, creatine monohydrate, in foods for particular nutritional uses, is not a matter of concern provided that there is adequate control of the purity of this source of creatine with respect to dicyandiamide and dihydro-1,3,5-triazine derivatives.

The Panel endorses the previous opinion of the SCF that high loading doses of creatine should be avoided. Provided high purity creatine monohydrate is used in foods for particular nutritional uses, the Panel concurs with the previous opinion of the SCF that the consumption of doses of up to 3g/day of supplemental creatine, similar to the daily turnover rate of creatine, is unlikely to pose any risk.

DOCUMENTATION PROVIDED TO EFSA

Letter from the European Commission to the Chairman of the Scientific Committee on Food on commission request for a specific opinion on the evaluation of a number of substances added for specific nutritional uses in foods for particular nutritional uses. SANCO D4/AN/dlc-D(2003)440384

Submission by IDACE (Paris, France) in reference to Commission Directive 2001/15/EC on substances that may be added for specific nutritional uses on foods for particular nutritional uses. Title: Creatine monohydrate dossier. Paris 2003

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* Declaration of interest see minutes of the 5th meeting of the AFC Panel held on 16 and 17 February 2004. These can be found at http://www.efsa.eu.int/science/afc/afc_meetings/catindex_en.html